

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

## PCT

### WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/EP2004/006654

International filing date (day/month/year)  
19.06.2004

Priority date (day/month/year)  
24.07.2003

International Patent Classification (IPC) or both national classification and IPC  
C07C227/16, C07C229/28, C07C213/08, C07C215/20, C07D211/32, C07D211/02

Applicant  
DEGUSSA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/006654

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material:  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing:  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/006654

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**Box No. II Priority**

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1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-9
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-9
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 The following documents are referred to in this communication:

- D1 : DEVANT R ET AL: "STEREOSELEKTIVE ALDOLREAKTION MIT CHIRALEN SEKUNDAEREN ACETAMIDEN STEREOSELECTIVE ALDOL REACTION WITH CHIRAL SECONDARY ACETAMIDES" CHEMISCHE BERICHTE, VERLAG CHEMIE GMBH. WEINHEIM, DE, vol. 119, 1 July 1986 (1986-07-01), pages 2191-2207, XP000608390 ISSN: 0009-2940
- D2 : HAYASHI T ET AL: "CHIRAL (BETA-AMINOALKYL)PHOSPHINES. HIGHLY EFFICIENT PHOSPHINE LIGANDS FOR CATALYTIC ASYMMETRIC GRIGNARD CROSS-COUPPLING" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 48, no. 13, 1983, pages 2195-2202, XP000881116 ISSN: 0022-3263
- D3 : SCHUDA P F ET AL: "A SHORT AND EFFICIENT SYNTHESIS OF (3S,4S)-4-U(TERT-BUTYLOXYCARBONYL) AMINO-5-CYCLOHEXUL-3-HYDROXPENTANOIC ACID ETHYL ESTER" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 53, no. 4, 1988, pages 873-875, XP002042034 ISSN: 0022-3263
- D4 : FAUSTINI F ET AL: "STEREOSPECIFICITY IN THE TRANSFORMATION OF ALPHA-AMINOACIDS INTO FLUOROACIDS" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 22, no. 45, 1981, pages 4533-4536, XP002072792 ISSN: 0040-4039
- D5 : D.J. PLATA ET AL: "The Stereospecific Preparation of an Hydroxyethylene Isostere Precursor Via a Novel Piperidine-2,5-Dione Template" TETRAHEDRON LETTERS, vol. 32, no. 30, 1991, pages 3623-3626, XP002307989
- D6 : S.E.DENMARK: "asymetric Construction of Quaternary Centers by Enantioselective Allylation: Application to the Synthesis of the Serotonin Antagonist LY426965" ORGANIC LETTERS, vol. 4, no. 11, 2002, pages 1951-1953, XP002307990

The present application does not meet the criteria of Article 33(1) PCT, because

the subject matter of claim 1 does not involve an inventive step in the sense of Article 33(3)PCT.

D1 discloses the preparation of R-cyclohexylglycin from R-phenylglycin in the presence of  $H_2/PtO_2$  in AcOH (see preparation 13--->23 p.2205).

D2 discloses the same preparation in the presence of  $H_2/Rh$  black.

From D1 and D2, the skilled person knows that a R-cyclohexyl glycine can be obtained from the corresponding R-phenylglycine with no racemisation either with a platinum-based catalyst or a rhodium-based catalyst. If both catalysts work, a combination thereof necessarily works as well and a skilled person wishing to develop an alternative process would have tried a catalyst based on the mixture.

For an inventive step to be acknowledged, the combination of catalysts must show an unexpected synergetic effect over each of the catalyst taken individually . This can be achieved by providing comparative tests.

The same argumentation applies with D3 or D5 in combination with D4 (preparation of cyclohexyl alanine).

The subject-matter of claims 2-9 does not contains any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

D6 discloses a preparation of N-protected d-piperidyl alanine from N-protected d-pyridil alanine with  $PtO_2/H_2$ .